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Abstract

Objectives: to evaluate the volumetric changes and peri-implant health at implant sites with and without previous soft tissue grafting over a 5-year observation period.

Materials and methods: In 18 partially edentulous patients, dental implants were placed in the esthetic zone (15-25) with simultaneous guided bone regeneration, followed by submerged healing. During the healing phase, eight patients (test) received a subepithelial connective tissue graft, whereas 10 patients (control) did not receive any soft tissue augmentation. Subsequently, abutment connection was performed and final reconstructions were inserted. Impressions were taken 1 week after crown insertion and at 5 years. Obtained casts were scanned and superimposed for volumetric and linear measurements. The mean distance (MD) in the mid-buccal area between the two surfaces and the differences in buccal marginal mucosal level ($bMML_{change}$) and in ridge width (RW_{change}) were evaluated. Peri-implant health was assessed using probing pocket depth (PPD) values, plaque index (PlI) and bleeding on probing (BOP).

Results: At a median follow-up time of 60.5 months a median MD of -0.38 mm (Min: -0.94; Max: -0.03) (test) and of -0.51 mm (Min: -0.76; Max: 0.05) (control) was calculated. The level of the margo mucosae ($bMML_{change}$) demonstrated a median loss of -0.42 mm (Min: -1.1; Max: -0.01) (test) and of -0.33 mm (Min: -1.02; Max: 0.00) (control). The median RW_{change} ranged between -0.44 mm and -0.73 mm (test) and between -0.49 mm and -0.54 mm (control). Mean PPD values slightly increased, whereas PlI and BOP remained stable over time in both groups. None of the comparisons between the groups revealed statistically significant differences ($p>0.35$). A small sample size must be considered, however.

Conclusions: Limited by a retrospective case-control study design, implant sites with and without soft tissue grafting on the buccal side revealed only minimal volumetric and linear changes and stability of peri-implant parameters over 5 years.

Introduction

Following tooth extraction, remodeling processes are initiated leading to morphological changes of the surrounding soft and hard tissues (Araujo & Lindhe 2005). A regeneration of the missing volume is inevitable for implant treatment in the esthetic zone. In order to achieve an optimal tissue volume, an augmentation of the hard as well as of the soft tissues appears to be a prerequisite (Schneider, et al. 2011).

Guided bone regeneration (GBR) is a predictable treatment modality to regenerate bone (Buser, et al. 1990). Moreover, implant survival rates are reported to be high irrespective of whether implants were placed in native or in augmented bone (Hammerle, et al. 2002). GBR has further shown to be effective to regenerate volume along the mucosal margin in terms of tissue height and thickness (Benic, et al. 2016).

Apart from hard tissue augmentation, soft tissue volume augmentation is considered a frequently used step during implant therapy in the esthetic zone. Soft tissue volume augmentation is usually carried out by the use of a subepithelial connective tissue graft (SCTG), a technique described in the 80ies (Langer & Calagna 1982). Many studies using SCTGs were performed for root coverage procedures (Cairo, et al. 2008, Cheng, et al. 2015), for gain of keratinized tissue or for pontic sites (Gonzalez-Martin, et al. 2014, Sanz-Martin, et al. 2016). SCTG were also used in conjunction with dental implant placement, either simultaneously or during the healing phase of the implant. Beneficial outcomes in terms of the soft tissue contour, esthetics and the facial mucosal level were reported at implant sites (Boardman, et al. 2015, Migliorati, et al. 2015, Yoshino, et al. 2014).

Various methods have been described in the literature to assess esthetic outcomes of implants, peri-implant tissues and implant-supported reconstructions. This included analyses of the clinical crown height, the extent of recession (Chambrone, et al. 2008), the white esthetic score (Belser, et al. 2009), the pink esthetic score (Furhauser, et al. 2005) and the papilla fill (Jemt 1997). From a clinical point of view, a three-dimensional analysis monitoring the changes of the peri-implant tissues over time is desired. Data on volumetric changes of the peri-implant tissues, however, are still limited to one-year reports (De Bruyckere, et al. 2015, Schneider, et al. 2011).

Moreover, no information is available in the literature assessing the effect of soft tissue augmentation procedures at implant sites with a longer follow-up.

Apart from volumetric and linear changes that predominantly assess the peri-implant tissues from an esthetic point of view and do not reflect the health status, the long-term periodontal status of implant sites is of scientific interest. From a biologic point of view, it is unknown whether or not soft tissue volume grafting at implant sites results in a more favorable biologic response than untreated controls.

The aim of the present study was, therefore, to evaluate three- and two-dimensional changes and the peri-implant health at implant sites with or without soft tissue grafting over a 5-year observation period.

Materials and methods

Study design

This study was designed as a retrospective case-control study. Partially edentulous patients with dental implants placed in the esthetic area of the maxilla were selected from a patient pool reported in an earlier randomized controlled clinical trial (Thoma, et al. 2014), conducted at the Clinic of Fixed and Removable Prosthodontics and Dental Material Science, Center of Dental Medicine, University of Zurich, Switzerland. Following approval by the local ethical committee, patients had received implant therapy between the years 2002 and 2005. Detailed in- and exclusion criteria were reported earlier (Thoma, et al. 2014). For the present study, only patients with a fixed reconstruction and at least one implant in the esthetic region 15-25 were included. In case, patients had received more than one implant eligible for the study, one site was randomly selected. Out of this patient pool, 18 patients could finally be included. Eight patients had received a SCTG 4-6 weeks prior to abutment connection (test), whereas 10 patients did not receive any soft tissue volume augmentation during implant therapy (control).

Surgical procedures

In all 18 patients, dental implant placement was performed according to the standard of care at the Clinic of Fixed and Removable Prosthodontics and Dental Material Science. GBR procedures were performed at all 18 implant sites simultaneously with dental implant placement. Deproteinized bovine bone mineral (DBBM) (Bio-Oss® Granules or Bio-Oss Collagen®; Geistlich Pharma AG, Wolhusen, Switzerland) and a collagen membrane (Bio-Gide®; Geistlich Pharma AG) were used in all cases for GBR. Three to four months after implant placement, patients of the test group received a SCTG (Figure 1a-f), and abutment connection was performed 4-6 weeks later. In the control group, abutment connection was performed 3-4 months after implant placement. The decision to perform an additional soft tissue volume augmentation was based on esthetic reasons, mainly including a volume deficit on the buccal side of the implants and depending on whether or not the patients agreed on the additional procedure. The decision was not based on a biological reason and implant surfaces were supposed to be surrounded by bony

structures after the GBR procedure. Soft tissue volume augmentation was performed using a full-flap crestal approach on top of the implant including an elevation of the papillae, merging into a split thickness flap at the buccal aspect (Thoma, et al. 2016) or a minimally invasive approach without elevating the papillae. In brief, a pouch was prepared according to the expected size of the transplant using either sulcular incisions and a crestal incision connecting the palatal line angles of the adjacent teeth or a minimally invasive approach without elevation of the papillae (Figures 1e+f). A split thickness flap was then prepared, leaving the periosteum attached to the bone. Subsequently, a SCTG (Figure 1c), harvested from the palate by means of a single incision technique (Figure 1d), was placed into the vestibular pocket (Figures 1e+f). The donor site was closed by a cross-section suture (Gore-tex® 5-0 sutures, W.L. Gore & Associates, Flagstaff, AZ, USA).

Abutment connection was performed 3-4 months after implant placement (control) or 4-6 weeks after soft tissue augmentation (test) following the same protocol for all patients. Subsequently, for all implants screw-retained fixed single crowns or fixed dental prostheses were fabricated and inserted.

Clinical examinations

All patients were included in a regular maintenance interval at the Clinic of Fixed and Removable Prosthodontics and Dental Material Science. Follow-up examinations were scheduled one week after the insertion of the final reconstruction (baseline) and then yearly up to 5 years (5Y). At baseline and at 5 years (Figure 1g+h), a thorough clinical examination was performed (Thoma, et al. 2014). Moreover, alginate impressions of the implant sites were taken.

Processing of casts, image acquisition and matching of stereolithographic models

The casts (baseline, 5Y) made of dental stone were examined meticulously for irregularities at the implant site, along the buccal mucosal margin and the apical region, as well as in the papilla regions. All casts were then scanned with a desktop 3D scanner (Imetric 3D, Courgenay, Switzerland). The obtained stereolithographic files (standard tessellation language, STL) were imported into an image analysis software (Swissmeda Software, Swissmeda AG, Zurich,

Switzerland). The baseline and 5Y STL files were automatically superimposed by the software program and thereafter manually adjusted for optimal superimposition of the implant site (Figure 2).

Data evaluation

Two calibrated examiners independently performed all measurements on the superimposed STL files. Both researchers were experienced in performing this type of analysis. Variables in terms of peri-implant health were recorded at the clinical examinations according to a previously described protocol (Thoma, et al. 2014).

Volumetric measurements:

At the buccal aspect of the implant site, a region of interest (ROI) was selected according to a protocol described previously (Sanz Martin, et al. 2016, Schneider, et al. 2011). The ROI represented the esthetically critical area at implant sites as well as the area, where the SCTG was placed (in case soft tissue augmentation was performed). The coronal border of the ROI was selected 1mm below the mucosal margin of the baseline scan, the apical border at 5mm below the mucosal margin. The locations of the mesial and distal borders varied between the sites, but were standardized to 1mm apart from the contact point of the adjacent teeth (Figure 3). The software calculated the area of the selected ROI, the volume between the two surfaces and the mean distance between the surfaces (baseline and 5Y). As the volume is highly dependent on the size of the selected area, the data is expressed as mean distance (mm; MD).

Linear measurements:

A cross-section, representing the central implant axis, was selected to measure the crown height, representing the distance between the incisal edge of the baseline STL file to the buccal mucosal margin at baseline and at 5Y. One measurement point was placed at the incisal edge of the baseline model. From this point, the first measurement was done to the mucosal margin at baseline and the second to the margin at 5 years. The differences between the two measurements/time-points represent the change of the buccal marginal mucosal level (mm;

bMML$_{change}$) (Figure 4a). The ridge width at the buccal aspect of the implant was measured using the same cross-section at baseline and at 5y. Measurements were performed horizontally at three levels below the mucosal margin: 1mm (mm; RW1$_{change}$), 3mm (mm; RW3$_{change}$) and 5mm (mm; RW5$_{change}$) (Figure 4b). These measurements represented changes in peri-implant tissue thickness.

Papilla index:

The papilla index (Jemt 1997) was evaluated on both (baseline, 5Y) STL files separately for the mesial (PI$_{mesial}$) and distal papilla (PI$_{distal}$). This index includes the following scoring system: 0= no papilla present, 1= less than half of the height of the papilla present, 2= half or more of the papilla present, 3= papilla fills up the entire proximal space, 4= hyperplastic papilla.

Peri-implant health:

The health of the peri-implant tissues was assessed by recordings of probing pocket depth values (PPD, mm), bleeding on probing (BOP, positive or negative, %) and plaque index (PlI, positive or negative, %) at six sites per implant at baseline and at the 5-year follow-up. Healthy tissues are defined by absence of BOP and PPD <6mm.

Statistical analysis

Data were recorded in Excel (Microsoft Corporation, Redmond, Washington, USA) and statistical analysis was performed with SAS 9.4 (SAS Corp., Cary NC. USA). The differences between the two examiners (VS and SB) were analyzed by Wilcoxon signed rank test. An intergroup comparison between the medians of the test and control group was performed by Wilcoxon-Mann-Whitney test. The influence of the site was tested for side as well as anterior-posterior. Hodges-Lehmann estimation (HLest) and Spearman's rank correlation were performed. The Hodges-Lehmann-estimation of the differences between the groups and corresponding nonparametric confidence intervals are presented in table 1 of the appendix. The level of significance was set at 5%.

Results

Seven male and 11 female patients with a median age of 59.4 years (Min: 27; Max: 76.6) at the 5-year follow-up completed the investigation with a median follow-up time of 60.5 months (Min: 53; Max: 152). There were two smokers in the study population, both belonging to the control group. No complications occurred in all included patients and implant sites during the follow-up period. No statistically significant effect of the site was found ($p>0.114$). The differences between the two examiners (VS and SB) were determined by Wilcoxon signed rank test and were not statistically significantly different with p-values higher than 0.1231 (table 1). The averaged data measured by the two examiners in terms of MD, $bMML_{change}$ and RW_{change} are enlisted in table 2, and descriptive results of all assessed variables are shown in table 3.

Over the 5-year observation period, a median loss (MD) of -0.38 mm (Min: -0.94; Max: -0.03) in (test) and of -0.51 mm (Min: -0.76; Max: 0.05) (control) was observed. The buccal marginal mucosal level ($bMML_{change}$) exhibited a median loss of -0.42 mm (Min: -1.1; Max: -0.01) (test) and -0.33 mm (Min: -1.02; Max: 0.00) (control). Horizontally, minimal changes were recorded, representing a loss for $RW1_{change}$ of -0.73 mm (Min: -1.2; Max: 0.22) (test) and of -0.51 mm (Min: -1.35; Max: 0.00) (control). At 3 mm below the mucosal margin, the $RW3_{change}$ amounted to -0.44 mm (Min: -0.85; Max: -0.29) (test) and to -0.54 mm (Min: -1.1; Max: 0.19) (control). $RW5_{change}$ presented values of -0.59 mm (Min: -1.21; Max: 0.00) (test) and of -0.49 mm (Min: -1.54; Max: 0.12) (control). The papilla index revealed a slight reduction over time at the mesial and distal papilla in both groups. All results demonstrated no statistically significant differences between the groups ($p>0.35$). The measurements of MD, CH_{change} and RW_{change} correlated since all correlations were between 0.684 and 0.88.

Median PPD was 3.20 mm (Min: 2.80; Max: 4.80) (test) and 2.75 mm (Min: 1.50; Max: 5.00) (control) at baseline and increased slightly to 3.67 mm (Min: 2.67; Max: 5.00) (test) and 3.33 mm (Min: 2.00; Max: 6.67) (control) at 5 years. The median values for BOP amounted 25% (Min: 0%; Max: 75%) (test) and 38% (Min: 0%; Max: 88%) (control) at baseline and measured 31% (Min: 13%; Max: 75%) (test) and 31% (Min: 0%; Max: 75%) (control) at 5 years. The

respective median values for PlI were 0% (Min: 0%; Max: 50%) (test) and 0% (Min: 0%; Max: 75%) (control) at baseline and 25% (Min: 0%; Max: 33%) (test) and 13% (Min: 0%; Max: 50%) (control) at 5 years. None of these differences between the groups were statistically significantly different between the groups at any time-point ($p>0.05$).

There were some missing data in terms of $RW5_{change}$ due to the fact that the variable could only be assessed if the level of measurement was within the keratinized tissue (coronal to the mucogingival junction). In one patient, PI distal was not assessed because the test site 15 was the last tooth in a shortened dental arch. Smoking was only reported at baseline and clinical parameters were missing for one patient belonging to the test group (respectively 2 patients for PlI).

Discussion

This retrospective controlled study evaluated the peri-implant tissue stability in patients treated with or without SCTG over an observation period of 5 years. The study demonstrated minimal changes in terms of i) mean distance in the selected buccal ROI ii) vertical and horizontal tissue reduction without statistically significant differences between the groups. These findings were supported by correlations found between volumetric and linear measurements. In addition, soft tissue volume augmentation at implant sites demonstrated neither a benefit nor a disadvantage in terms of the long-term biologic response.

The obtained data revealed a high consistency. The mean distance within the region of interest showed minimum and maximum values within 1 mm, the change of the buccal marginal mucosal level within 1.1 mm and the change of the ridge width within 1.7 mm. There was no trend for a higher variance in one of the groups with respect to all obtained variables. In general, a tissue loss of 0.5 mm of the buccal peri-implant tissues within 5 years was detected in both groups. This finding is in line with the results of other studies after a one-year follow-up (De Bruyckere, et al. 2015, Schneider, et al. 2011). Translating this into a clinical environment, 0.5 mm of loss might be considered as clinically acceptable in the esthetic region, keeping in mind that such minimal changes might not be perceived by the naked eye. One has to bear in mind that healthy tissues around natural teeth present changes over longer observation periods as well, but studies with comparable measurement techniques are not available. Measurement of an untreated site to obtain a positive control was rejected for two reasons: i) Contralateral teeth in the esthetic region were often affected by the treatment and therefore could not serve as an accurate control; ii) a comparison with posterior teeth would be affected by many additional factors.

The performed measurements, linear and volumetric, analyze the overall change of the peri-implant tissues. Thus, the combined effect of the soft and hard tissue changes was measured. As the study is focusing on the soft tissue, the hard tissue component had to be highly standardized. Only patients with GBR by means of a CM and DBBM at the time of implant placement were included in this study. At the time-point of baseline impression taking, the GBR

procedure was at least 4 months ago, and can be considered to be stable, as DBBM is documented to have a very low resorption rate (Araujo, et al. 2002). The materials used for GBR are reported to obtain high volume stability clinically (Buser, et al. 2013, Jensen, et al. 2014). Two patients were additionally in need of a prior bone augmentation by means of an autologous bone block. The results in terms of volume stability in these two cases were averaged and in line with the findings in other patients.

The soft tissues underlie changes as well, first due to the integration process at the recipient site, which is documented to occur during the first 4-6 weeks (Allen, et al. 1985, Rotenberg & Tatakis 2014, Studer, et al. 2000). Furthermore, major changes occur due to the treatment in terms of abutment connection and soft tissue conditioning by means of provisional crowns. At the time of the baseline impression, soft tissue grafting was at least 3 months ago. As the aim of this study was to assess long-term stability, not early changes, the time-point of impression taking can be considered to be ideal and cannot be chosen earlier due to changes caused by the prosthetic treatment.

Because the potential of SCTG is very high to replace missing tissue volume to a considerable extent (Bassetti, et al. 2016, Thoma, et al. 2014), this technique remains the gold standard for soft tissue augmentation in dentistry. Very different prerequisites for the soft tissue are present around dental implants compared to teeth, in terms of attachment to the surface, but also nutrition due to the missing periodontal ligament. The connective tissue gathered from the palate has proven a good integration at these sites regardless of these circumstances. Furthermore, this study provides further evidence that the soft tissues remain as stable as non-grafted sites on the long term, which justifies this treatment accompanied with a certain morbidity. From a patients perspective, the treatment with a SCTG is an intervention associated with a relatively high morbidity (Lorenzo, et al. 2012, Sanz, et al. 2009) and a solid volume gain and continuing stability are therefore of paramount importance.

The PI decreased minimally over time for the mesial and distal values in both groups. This finding is in contradiction with studies reporting of an early recovery of the papilla within the first

years (Grunder 2000, Jemt 1997, Raes, et al. 2015). Eventually this might be due to the longer observation period in the present study. One might speculate that following an increase in the first year, changes in papilla height occurred between year 1 and year 5. Moreover, PI values were in general low in patients with adjacent implants (3 test, 1 control). This finding is reasonable as it is well documented that the creation of a papilla between implants is more difficult to achieve compared to sites with at least one neighboring (Tarnow, et al. 2003). No correlations were found between peri-implant tissue changes on the buccal side and changes of the papilla height.

The assessment of peri-implant health revealed, in general, healthy tissues with only two PPD values exceeding 5 mm. The obtained results are in line with findings in other studies, except for BOP, which, in both groups, appeared to have relatively high values. However, other studies found BOP values that were even higher at a 5-year follow-up (Becker, et al. 2016, Brandenberg, et al. 2016, van Velzen, et al. 2015).

The present results are limited by the following facts: i) retrospective study design ii) small sample size iii) data were extracted from a RCT comparing two implant systems, without focusing on soft and hard tissue augmentations at that time, even if the site seemed not to have an impact on the outcome variables according to the statistical test.

Conclusion

Implant sites with and without soft tissue grafting on the buccal side revealed only minimal changes over 5 years based on volumetric and linear outcome measures without significant differences between the two groups. Periodontal parameters remained stable over time. The use of a SCTG based on an esthetic indication resulted in similar biological outcomes compared to non-grafted implant sites. The small sample size and retrospective study design must be taken into account when drawing conclusions and recommendations for clinicians.

Acknowledgements and conflict of interest

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Figure legend

Figure 1a+b Buccal and occlusal view of a healed ridge with remaining volume deficiency after implant placement with simultaneous guided bone regeneration.

Figure 1c Subepithelial connective tissue graft.

Figure 1d The donor site after suturing.

Figure 1e+f Buccal and occlusal view after placement of the subepithelial connective tissue graft into the prepared pouch.

Figure 1g Reexamination one week after insertion of the final restoration, time-point of baseline impression taking.

Figure 1h The site at the 5-year follow-up examination, where the second impression was taken.

Figure 2 The stereolithographic files from baseline (yellow) and 5-year follow-up (green) are superimposed.

Figure 3 Illustrative image of the measured volume (blue) at tooth 21 on the 5-year follow-up surface (green).

Figure 4a Cross-section of tooth 21 from figure 2+3. The crown height was measured to evaluate the difference in buccal marginal mucosal level ($bMML_{change}$) between baseline and 5Y, using the same incisal reference point on the baseline surface.

Figure 4b The same cross-section was used in order to measure the difference of the ridge width at 1 mm, 3 mm and 5 mm below the buccal mucosal margin.

Table 1 The table shows the results of the Wilcoxon signed rank test in order to compare the two examiners. Lowest p-value was p=0.1231. N = number, SD = standard deviation, Min = minimum, Q1 = 25% quartile, Q3 = 75% quartile, Max = maximum, PROB = probability (p-value), bMML = buccal marginal mucosal level, RW = ridge width, PI = papilla index.

Table 2 All measurements in terms of mean distance (MD), buccal marginal mucosal level ($bMML_{change}$) and ridge width (RW_{change}) are presented case by case. As table 1 did not reveal

statistically significant differences between the two examiners, the means of both measurements are shown. CM = collagen membrane, DBBM = deproteinized bovine bone mineral, IP = implant placement, AB = autologous bone block

Table 3 Descriptive data for all evaluated variables. The mean of both examiners is shown. N = number, SD = standard deviation, Min = minimum, Q1 = 25% quartile, Q3 = 75% quartile, Max = maximum, bMML = buccal marginal mucosal level, RW = ridge width, PI = papilla index, PPD = probing pocket depth, BOP = bleeding on probing, PlI = plaque index.

Appendix table 1 Hodges-lehmann-estimation (HLest) of the differences between the groups and corresponding nonparametric confidence intervals (95% CI). bMML = buccal marginal mucosal level, RW = ridge width, PI = papilla index.

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Group	Variable	N	Mean	SD	Min	Q1	Median	Q3	Max
control	Mean distance (mm)	10	-0.35	0.32	-0.76	-0.58	-0.51	-0.01	0.05
control	$bMML_{change}$ (mm)	10	-0.35	0.30	-1.02	-0.47	-0.33	-0.11	0.00
control	$RW1_{change}$ (mm)	10	-0.52	0.44	-1.35	-0.70	-0.51	-0.17	0.00
control	$RW3_{change}$ (mm)	10	-0.41	0.41	-1.10	-0.69	-0.54	0.00	0.19
control	$RW5_{change}$ (mm)	8	-0.52	0.52	-1.54	-0.74	-0.49	-0.16	0.12
control	PI_{mesial} baseline	10	1.85	0.67	1.00	1.00	2.00	2.00	3.00
control	PI_{distal} baseline	9	1.61	0.65	1.00	1.00	1.50	2.00	2.50
control	PI_{mesial} 5Y	10	1.70	0.63	1.00	1.00	2.00	2.00	2.50
control	PI_{distal} 5Y	9	1.39	0.78	0.00	1.00	1.00	2.00	2.50
control	PPD baseline (mm)	10	2.76	0.92	1.50	2.30	2.75	3.00	5.00
control	PPD 5Y (mm)	10	3.65	1.38	2.00	3.00	3.33	3.50	6.67
control	BOP baseline (%)	10	35	30	0	0	38	56	88
control	BOP 5Y (%)	10	38	29	0	25	31	75	75
control	PlI baseline (%)	10	14	24	0	0	0	25	75
control	PlI 5Y (%)	10	14	17	0	0	13	25	50
control	Smoking baseline (%)	10	20	42	0	0	0	0	100
test	Mean distance (mm)	8	-0.44	0.28	-0.94	-0.61	-0.38	-0.29	-0.03
test	$bMML_{change}$ (mm)	8	-0.47	0.32	-1.10	-0.61	-0.42	-0.31	-0.01
test	$RW1_{change}$ (mm)	8	-0.62	0.45	-1.20	-0.91	-0.73	-0.36	0.22
test	$RW3_{change}$ (mm)	8	-0.50	0.20	-0.85	-0.62	-0.44	-0.38	-0.29
test	$RW5_{change}$ (mm)	7	-0.60	0.42	-1.21	-1.05	-0.59	-0.34	0.00
test	PI_{mesial} baseline	8	1.56	1.05	0.00	0.75	2.00	2.00	3.00
test	PI_{distal} baseline	8	1.56	1.24	0.00	0.25	2.00	2.50	3.00
test	PI_{mesial} 5Y	8	1.44	1.12	0.00	0.50	1.50	2.25	3.00
test	PI_{distal} 5Y	8	1.31	1.03	0.00	0.50	1.25	2.00	3.00
test	PPD baseline (mm)	7	3.45	0.66	2.80	3.00	3.20	3.67	4.80
test	PPD 5Y (mm)	7	3.67	0.79	2.67	3.00	3.67	4.33	5.00
test	BOP baseline (%)	7	35	30	0	16	25	75	75
test	BOP 5Y (%)	7	38	26	13	13	31	67	75
test	PlI baseline (%)	6	8	20	0	0	0	0	50
test	PlI 5Y (%)	6	10	15	0	0	0	25	33
test	Smoking baseline (%)	6	0	0	0	0	0	0	0

Subject number	Group	Site	GBR Procedure	Mean distance (mm)	$bMML_{change}$ (mm)	$RW1_{change}$ (mm)	$RW3_{change}$ (mm)	$RW5_{change}$ (mm)
1	control	14	CM and DBBM	0.05	0.00	0.00	0.00	0.00
2	control	14	CM and DBBM	-0.56	-1.02	-1.35	-0.59	
3	control	24	CM and DBBM	-0.60	-0.60	-0.62	-0.51	-0.78
4	control	14	CM and DBBM	-0.76	-0.47	-1.10	-1.10	-1.54
5	control	15	CM and DBBM	-0.01	-0.37	-0.17	0.00	
6	control	12	CM and DBBM	0.04	-0.29	-0.11	0.19	0.12
7	control	24	CM and DBBM	-0.03	-0.05	-0.17	-0.07	-0.32
8	control	14	CM and DBBM	-0.51	-0.12	-0.52	-0.57	-0.70
9	control	21	CM and DBBM	-0.51	-0.18	-0.70	-0.72	-0.42
10	control	15	CM and DBBM	-0.58	-0.40	-0.50	-0.69	-0.55
11	test	12	CM and DBBM	-0.94	-0.38	-0.82	-0.78	-1.05
12	test	11	CM and DBBM	-0.30	-0.31	-0.46	-0.46	-0.59
13	test	21	AB prior to IP, CM and DBBM at IP	-0.28	-0.32	-0.26	-0.29	-0.34
14	test	11	CM and DBBM	-0.42	-0.46	-0.65	-0.44	
15	test	22	CM and DBBM	-0.70	-1.10	-1.20	-0.85	-1.21
16	test	21	CM and DBBM	-0.34	-0.49	-0.88	-0.42	-0.35
17	test	14	CM and DBBM	-0.03	-0.02	0.22	-0.44	-0.67
18	test	22	AB prior to IP, CM and DBBM at IP	-0.53	-0.74	-0.95	-0.34	0.00

Variable	N	Mean	SD	Min	Q1	Median	Q3	Max	W_SGNR	PROB
Mean distance	18	0,01	0,06	-0.14	-0.02	0.02	0.05	0.15	20,5	0.2584
$bMML_{change}$	18	-0,02	0,16	-0.42	-0.11	0.01	0.05	0.23	2,5	0.9275
$RW1_{change}$	18	-0,07	0,20	-0.56	-0.20	-0.08	0.04	0.25	-33	0.1231
$RW3_{change}$	18	-0,02	0,07	-0.21	-0.03	0.00	0.01	0.07	-10	0.5519
$RW5_{change}$	15	0,02	0,16	-0.24	-0.04	0.02	0.06	0.39	8,5	0.5313
PI_{mesial} baseline	18	-0,11	0,32	-1.00	0.00	0.00	0.00	0.00	-1,5	0.5000
PI_{distal} baseline	17	-0,24	0,44	-1.00	0.00	0.00	0.00	0.00	-5	0.1250
PI_{mesial} 5Y	18	-0,06	0,42	-1.00	0.00	0.00	0.00	1.00	-1	1.0000
PI_{distal} 5Y	17	-0,12	0,33	-1.00	0.00	0.00	0.00	0.00	-1,5	0.5000

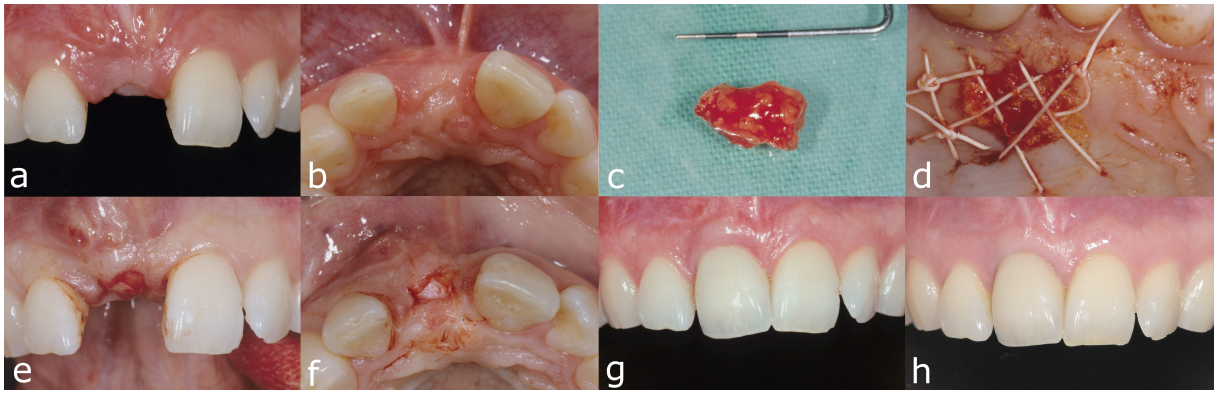

Figure 1

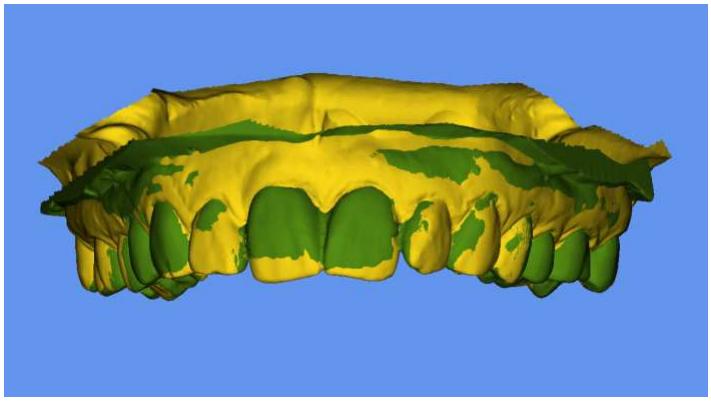

Figure 2

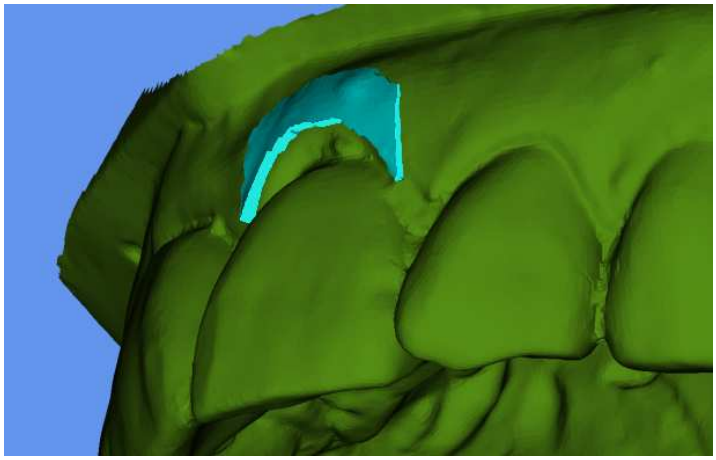

Figure 3

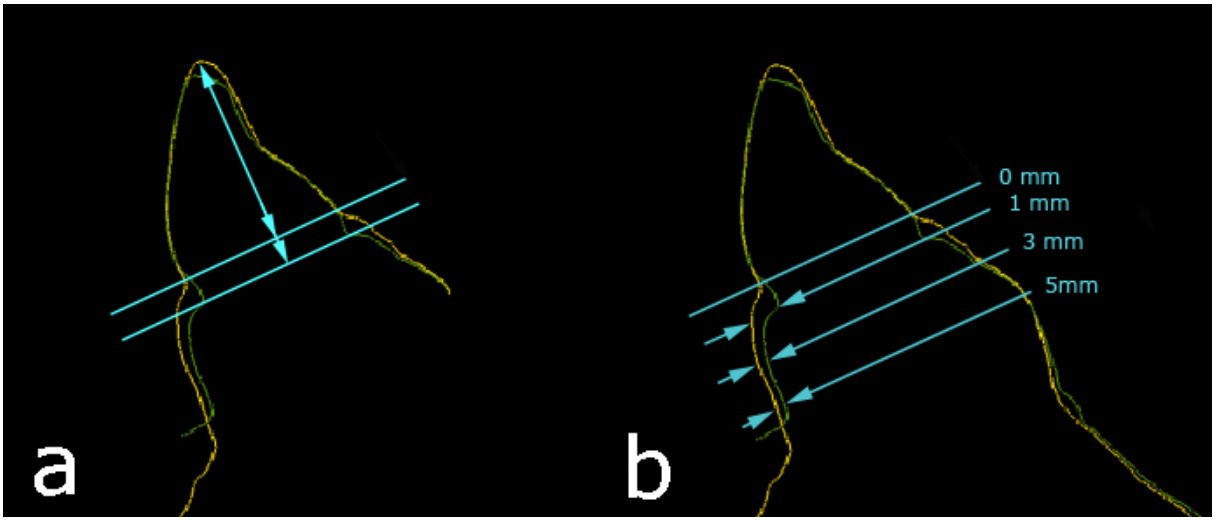

Figure 4

Variable	HLest	lower_cl 95%	upper_cl 95%
Mean distance (mm)	0.065	-0.245	0.390
$bMML_{change}$ (mm)	0.128	-0.155	0.410
$RW1_{change}$ (mm)	0.163	-0.385	0.650
$RW3_{change}$ (mm)	0.108	-0.260	0.435
$RW5_{change}$ (mm)	0.080	-0.425	0.660
PI_{mesial} baseline	0.000	-1.000	1.000
PI_{distal} baseline	0.000	-1.000	1.000
PI_{mesial} 5Y	0.000	-1.000	1.000
PI_{distal} 5Y	0.000	-1.000	1.000